Comparison of the efficacy of long-term treatment of primary monosymptomatic nocturnal enuresis of varying severity using traditional methods

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Abstract

Background: Primary monosymptomatic nocturnal enuresis (PMNE) is a pathological state where the patient has no problem with bladder control in the waking state but does not awake from the urge to urinate. Very little is known about the prognostic factors regarding effective treatment of PMNE using methods recommended by the International Children's Continence Society.

Objective: To compare the efficacy of long term treatment of PMNE using alarm intervention (AI) and desmopressin in children and adolescents and also to study the impact on it of the severity of disease, age and socio-economic factors.

Method: Study was conducted from 15th January to 30th October, 2016 in the Far Eastern Federal University (Vladivostok) in children 7 to 14 years old having PMNE. At the preliminary stage, the clinical, socio-economic and demographic characteristics of the children were noted. All patients had blood and urine tests done and the level of antidiuretic hormone was determined. To exclude a hyperactive bladder, uroflowmetry and a questionnaire survey of OABq-SF were used. Monitoring of changes in the number of episodes of enuresis (EE) and independent awakenings was carried out using a voiding diary. In the active phase of the study, patients from group A underwent treatment by AI and patients from group B received desmopressin 0.4 mg per day.

Results: There were 339 children aged 7 to 14 years with PMNE during the study period. Group A comprised 162 children treated with AI. At the end of the 4-month course, absence of PMNE was noted in 82.7% patients and after 6 months in 74.7% children. Group B comprised 177 children treated with desmopressin 0.4 mg/day. In group B the absence of PMNE was noted 4 months after the start of the experiment in 72.9% of children and after six months in 67.2% of children. Construction of a two-stage regression model and carrying out partial F-tests established that in group A, the EE level was significantly associated with age ($p<0.05$), and the severity of symptoms ($p<0.01$). In group B, the EE level was associated with age ($p<0.05$) and severity of symptoms ($p<0.05$). In addition, it was found that the effectiveness of AI was significantly higher in children who had a greater number of independent awakenings before treatment ($p\leq0.01$).

Conclusions: Use of AI in the treatment of PMNE is significantly associated with the number of independent awakenings. Use of both AI and desmopressin are significantly associated with age and severity of symptoms of PMNE. Socio-economic and demographic factors have no significant influence on treatment outcomes of PMNE.

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(Key words: Enuresis, alarm intervention, desmopressin, effectiveness, predictors, treatment)

Introduction

Primary monosymptomatic nocturnal enuresis (PMNE) is a pathological state where the patient has no problem with bladder control in the waking state but does not awake from the urge to urinate. The incidence of PMNE in the population is 15-16% in the 5-9 year olds, 4-6% in the 10-12 year olds, about 1.5% in 14-year-olds and less than 1% among adults[1-5]. The aetiological factors of primary enuresis include delay in forming a nerve urination regulatory mechanism, disturbances of antidiuretic hormone synthesis, violation of the sleep-wake cycle and sleep characteristics or some other pathological condition[6-8].

International Children's Continence Society (ICCS)[9] and National Clinical Guideline Centre

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(NCGC), UK, in 2012 presented the clinical recommendations for diagnosis and treatment of PMNE. According to these, the main methods for active treatment of enuresis are alarm intervention (AI) and desmopressin. Both methods are considered safe and their effectiveness is estimated at 60-90%[6,10]. AI entails the use of special alarm devices that awaken the patient at the beginning of urination[11]. Desmopressin reduces night diuresis, thereby reducing the number of 'wet' nights[12]. However, search for new effective treatment for PMNE continues. In particular, antimuscarinic drugs (AMDs) have been tested[13]. It is known that AMDs increase the volume of the bladder and time between urges to urinate[14-16]. However, results from the use of AMDs in the treatment of enuresis are contradictory[17]. For the treatment of PMNE in clinical practice, AI, desmopressin and their combination continue to be used[18]. According to some researchers[19] and our earlier studies[20,21], effect of treatment with AI comes later than when using desmopressin or a combination of AI and desmopressin. Combination therapy using AI and desmopressin is not significantly better than using each method separately.

In addition, studies of predictors for treatment effectiveness with each method are scarce according to Scopus, WoS and PubMed. In the literature, there is fragmented evidence that the efficacy of desmopressin is higher in older children having a small number of 'wet nights' and nocturnal polyuria[22]. Other researchers indicate that the efficacy of desmopressin is related to the frequency and severity of symptoms, motivation of children[19,23] and adherence to treatment[24]. These results appear rational but have so far not been carried out in a comprehensive study of predictors of effective treatment to PMNE, taking into account the influence of the initial clinical, demographic, socio-economic factors on the outcome of therapy using each particular method.

Objectives

To compare the efficacy of long term treatment of PMNE using alarm intervention (AI) and desmopressin in children and adolescents and also to study the impact on it of the severity of disease, age and socio-economic factors.

Method

The study was conducted from 15th January, 2016 to 30th October, 2016 in the urological centre of the city polyclinic No. 3 (Vladivostok), in the diagnostic department of Children's Medical Association No. 2 (Vladivostok) and Far Eastern Federal University (Vladivostok) on children aged 7 to 14 years with PMNE. The children were randomly divided into two groups: Group A comprised children treated by alarm intervention (AI) and Group B comprised children treated with desmopressin 0.4 mg/day. To randomize patients, the method of blind random sample was used. The study included patients with urination during sleep (at least twice a week)[6,7,9], who previously had not used AI or taken desmopressin. Clinical, socio-economic and demographic characteristics of the children are shown in Table 1.

A detailed history was taken in children who complained of urination during sleep of demographic data and socio-economic status (SES) of the children and their families. Laboratory tests included blood tests, urinalysis, stool analysis and measurement of urinary flow rate using uroflowmetry. Using the overactive bladder questionnaire (OABq-SF), the presence of overactive bladder (OAB) symptoms was detected. Throughout the study, children, together with their parents or caretakers, filled out the voiding diary, supplemented with graphs that indicated the number of episodes of enuresis (EE), the amount of fluid consumed, the numbers of self-awakening (SA) at urge to urinate, and also the report on treatment[25].

Exclusion criteria were the presence of OAB, acute inflammatory disease, chronic disease in the active stage and changed level of antidiuretic hormone in the blood (the norm was taken as <1.5ng/L with an osmolarity level of 270-280mosm/L). The treatment phase, according to ICCS recommendations, lasted 16 weeks. In group A the signal system of Wet Stop/ BYE-WET, PALCO LABS, Inc (USA) was used. Before treatment, patients, their parents, or caregivers were instructed about guidance on the use of alarm systems. In group B the therapeutic agent used was desmopressin in a dose of 0.4mg once a day. At this stage, patients with the help of their parents filled out a voiding diary, information from which was analysed in 8 weeks. Written informed consent was obtained from all parents prior to their children participating in the experiment. The total time of observation of the children was 16+8 = 24 weeks. The algorithm for the study is shown in Figure 1. The study protocol has been approved by the Ethics Committee of the Far Eastern Federal University.

Next, we assessed the effect of sex, age, presence of siblings, family completeness (one or two parents), family income level, level of education of parents, place of residence, severity of enuresis symptoms, number of 'dry nights' per week, number of urinations per day, number of self-awakenings at the urge to urinate and the clinical characteristics of urination on the effectiveness of the therapy. Under the severe symptoms of enuresis, we understood the availability of more than 5 episodes of enuresis per week.

Table 1: ***Clinical, demographic and socio-economic characteristics of children with PMNE***

Variable	Group A *(n=162)* Mean (SD) or No. (%)	Group B *(n=177)* Mean (SD) or No. (%)	Total *(n=339)* Mean (SD) or No. (%)
Gender			
Male	87 (53.7)	92 (51.9)	179 (52.8)
Female	75 (46.3)	85 (48.1)	160 (47.2)
Siblings	1.3 (0.7)	1.4 (0.4)	1.4 (0.7)
Full family (mother & father)	113 (69.7)	137 (77.4)	250 (73.7)
Age group			
6-8 years	57 (35.2)	55 (31.1)	112 (33.0)
9-11 years	54 (33.3)	59 (33.3)	113 (33.3)
12-14 years	51 (31.5)	63 (35.6)	114 (33.6)
Place of residence			
Village	83 (51.2)	88 (49.7)	171 (50.4)
City	79 (48.8)	89 (50.3)	168 (49.5)
**Average annual family income*			
<$2,830	23 (14.2)	14 (07.9)	37 (10.9)
$2,830-4,400	78 (48.1)	85 (48.0)	163 (48.1)
$4,400-15,884	34 (20.9)	31 (17.5)	65 (19.1)
$15,884+	27 (16.7)	47 (26.5)	74 (21.8)
***Parental education*			
< High School	09 (05.5)	05 (02.8)	14 (04.1)
High School	63 (38.8)	84 (47.4)	147 (43.4)
University degree	79 (48.7)	81 (45.7)	160 (47.2)
Master's degree or >	11 (06.7)	07 (03.9)	18 (05.3)
Leucocytes x 10^9/L	7.1 (2.0)	6.5 (2.5)	6.9 (2.3)
PPAF, pmol /L	3.71 (2.44)	3.98 (3.06)	4.83 (2.82)
Number of episodes enuresis / week	3.6 (0.9)	4.1 (1.1)	3.9 (1.3)
Number of episodes self-awakening	4.8 (1.5)	5.5 (1.8)	5.2 (1.9)
Number of dry nights	3.9 (2.3)	3.6 (1.7)	3.8 (2.1)
****Children with severe symptoms*	102 (62.9%)	126 (71.2%)	228 (67.2%)
Average number of urination/ day	7.8 (1.7)	7.2 (3.1)	7.5 (3.7)
Average flow rate ml/sec (uroflowmetry)	12.4 (6.9)	13.6 (4.7)	13.1 (6.2)
Maximum flow rate ml/sec (uroflowmetry)	14.7 (4.6)	14.9 (5.9)	14.7 (7.4)
Bladder volume, ml (uroflowmetry)	126.7 (23.6)	133 (17.9)	129.6 (21.7)

**$2,830- average minimum wage at time of study x 2, $4,400 - average living wage over same period x 2 and $16,455- average wage level in all spheres of economics over 2016 year; **At least one of the parents; ***More than 5 episodes a week*

PMNE: primary monosymptomatic nocturnal enuresis, SD: standard deviation, PPAF: posterior pituitary antidiuretic factor

The variance analysis (ANOVA) was used to estimate the reliability of the differences between mean values of compared parameters. Using the weighted least squares (WLS), we conducted a multivariate regression analysis to identify the relationships between SES variables, anthropological and clinical parameters, and the number of episodes of enuresis after treatment with different methods. Selection of incoming variable in the model specification was carried out by comparing the mean squares of regressions with mean squared errors (Fisher criterion). However, to explore the possibility of nonlinear dependencies, the final model included both incremental and non-increasing variables. All statistical analyses were performed using SAS version 8.0.2. $p<0.05$ was considered statistically significant.

Results

There were 339 children aged 7 to 14 years with PMNE during the study period. Group A comprised 162 children treated with AI. Group B comprised 177 children treated with reboxetine 0.4 mg/day. Table 2 presents the stepwise regression results of the number for episodes of enuresis (EE) under the influence of independent variables.

Table2: ***Number of episodes of enuresis regressed on each SES, demographic and clinical parameters separately and full sample (n=339)***

Variable	Measures on each variable separately		Measures for the full sample	
	Group A ***(n=162)*** **Estimate (SD)**	**Group B** ***(n=177)*** **Estimate (SD)**	**Group A** ***(n=162)*** **Estimate (SD)**	**Group B** ***(n=177)*** **Estimate (SD)**
Gender (Female)	-0.13 (0.07)	-0. 32 (0. 14)	-0.21 (0.18)	-0.13 (0.13)
Siblings 1 or less More than 1	 Reference group 0.25 (0.11)	 Reference group 0.31 (0.13)	 Reference group 0.03 (0.016)	 Reference group 0.041 (0.31)
Full family (mother and father)	-0.47 (0.29)	-0.10 (0.17)	-0.18 (0.14)	-0.9 (0.8)
Age group (years) 6-8 9-11 12-14	 Reference group -0.95** (0.26) -1.33** (0.32)	 Reference group -1.04* (0.36) -1.57** (0.39)	 Reference group -0.79* (0.23) -0.89* (0.46)	 Reference group -0.51 (0.49) -0.90* (0.52)
Place of residence City Village	 Reference group 0.07 (0.05)	 Reference group 0.11 (0.04)	 Reference group 0.03 (0.08)	 Reference group 0.04 (0.04)
R^2	7.9%	16.0%	17.8%	10.3%
Parent education (At least one parent) < High school High school > High school (University/ Master's degree)	 -0.12 (0.03) -0.12 (0.07) Reference group	 -0.22 (0.15) -0.31 (0.13) Reference group	 -0.09 (0.01) -0.16 (0.08) Reference group	 -0.24 (0.10) -0.13 (0.05) Reference group
R^2	11.4%	16.7%	18.9%	19.2%
Annual family income <$2830 $2830-4400 $4400-16455 $7942+	 -0.98* (0.035) -0.69 (0.047) -0.19 (0.09) Reference group	 -0.65 (0.18) -0.33 (0.24) -0.40 (0.25) Reference group	 -0.38 (0.09) -0.32 (0.06) -0.14 (0.18) Reference group	 -0.45 (0.18) -0.23 (0.20) -0.23 (0.15) Reference group
R^2	9.2%	8.8%	12.0%	3.9%
Severe symptoms (>5 episodes per week)	-2.15** (0.61)	-1.83** (0.57)	-1.58** (0.45)	-0.96* (0.27)
R^2	19.0%	17.9%	25.1%	18.9%
"Dry" night ≤ 3.8 > 3.8	0.52 (0.13) Reference group	0.34 (0.18) Reference group	0.57 (0.12) Reference group	0.29 (0.26) Reference group
R^2	9.3%	14.3%	13.7%	11.9%
Urination/ day ≤ 7.5 > 7.5	 Reference group -0.88* (0.21)	 Reference group -1.07** (0.39)	 Reference group -0.76 (0.56)	 Reference group -0.69 (0.37)
R^2	6.7%	10.6%	7.9%	
Self-awakening ≤ 5.2 > 5.2	 Reference group -2.21** (0.62)	 Reference group -0.57 (0.44)	 Reference group -1.17** (0.31)	 Reference group -0.33 (0.22)
R^2	25.6%	15.8%	12.1%	16.6%
Average flow rate ml/sec ≤13.1 >13.1	 Reference group -0.21 (0.15)	 Reference group -0.35 (0.17)	 Reference group -0.12 (0.10)	 Reference group -0.10 (0.13)
R^2	6.6%	9.2%	8.1%	7.5%
Bladder volume, ml ≤129 >129	 Reference group -0.36 (0.17)	 Reference group -0.24 (0.20)	 Reference group -0.27 (0.16)	 Reference group -0.15 (0.14)
R^2	12.4%	8.8%	9.5%	13.7%

*SES - socio-economic status; SD - standard deviation; 3.8 - average number of "dry" nights /week in the sample; 7.5 - average number of urination /day; 5.2 - number of episodes of self-awakening/week in the sample; * p<0.05,** p<0.01.*

The left part of the table presents the analysis results of the first step of regression for each anthropological, demographic, socioeconomic and clinical parameter. The number of EE in 6-8-year-old children after treatment became significantly less than in 9-11 year-olds (Group A p<0.001, Group B p<0.005), and in 12-14 year-olds (Group A p<0.001; Group B p<0.001). In both groups the number of EE after treatment was significantly lower in patients with severe symptoms than

among other patients (Group A p<0.001; Group B p<0.001). The number of EE in patients with higher number of urination after treatment decreased in Group A (p<0.05), and even more significantly in group B (p<0.001), as compared to control. In group A, the number of EE in children who often woke up independently (with urge to urinate) at the start of the study was significantly lower after treatment than in the rest of the patients (p<0.01); in group B, no such difference was found (p>0.05).

The conjugacy of SES parameters and other variables was studied using the level of EE and was also tested by using partial F-tests (not shown). Partial F-tests have confirmed that each variable value such as age, the severity of PMNE symptoms, the frequency of daytime urination, the number of episodes of independent awakenings, makes a significant contribution to the explanation of variance of EE.

In the right of the table are presented results of regression of EE for each anthropological, demographic, socio-economic and clinical parameter, taking into account the influence of all variables. Partial F-tests (not given) showed that in group A, the level of EE is associated with age (p<0.05), the number of independent awakenings (p<0.01) and the severity of symptoms (p<0.01). In group B, the EE level was also associated with age (p<0.05) and severity of symptoms (p<0.05).

Figure 1 demonstrates the dynamics of episodes of enuresis, independent awakenings with urge to urinate, and the number of 'dry' nights (for children from each group).

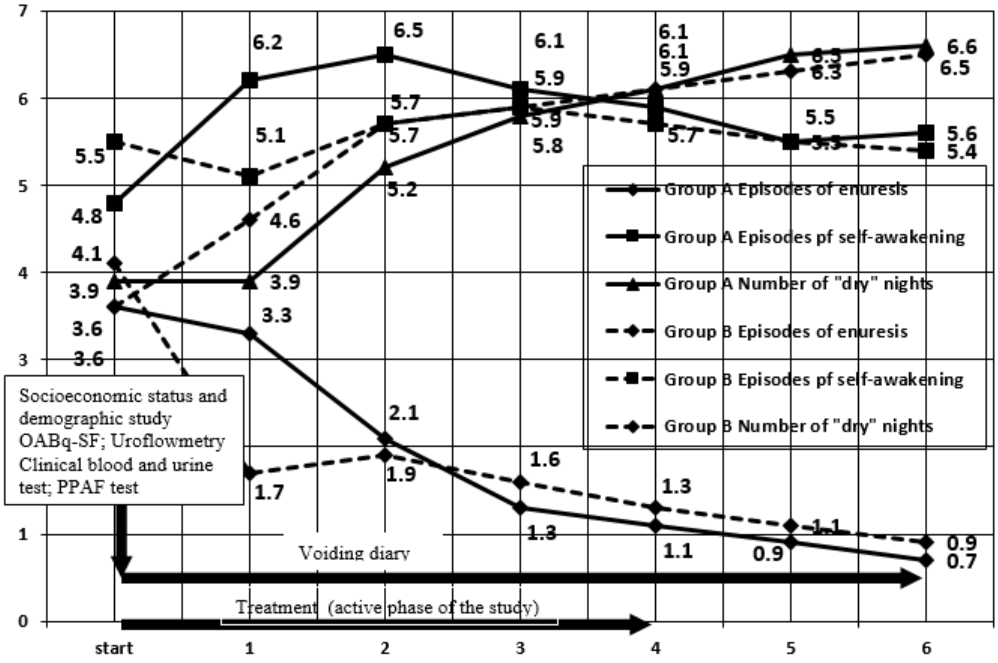

Figure 1: ***The change in frequency of episodes of enuresis, self-awakening and "dry" nights (per week) in group A (n= 162; Alarm therapy) and B (n= 177; receiving Desmopressin).***

After a month of treatment, the number of EE decreased sharply in children receiving desmopressin but remained almost unchanged in children who were prescribed AI therapy (3.3 vs. 1.7, p<0.05). However, in the period from 2 to 6 months of observation, differences between the numbers of EEs in the 2 groups remained within a range of statistical error. The number of episodes of independent awakenings and 'dry' nights in groups A and B increased slightly during the observation period but this was statistically insignificant.

In group A, the absence of PMNE was noted 4 months after the start of the experiment (the end of active phase) in 82.7% of children and after 6 months (the end of observation) in 74.7% of children. In group B the absence of PMNE was noted 4 months after start of experiment in 72.9% of children and after six months in 67.2% of children. Only 3 (0.9%) persons refused to participate in the study during it (all from group B).

Comparative analysis showed that the average level of investigated variables in group B was homogeneous for the complete and incomplete composition of the group. Children in group A did not complain about side effects during treatment. In Group B, 11 (6.2%) children complained of dry mouth and nausea, and in 2 (1.1%) cases - headache. All the symptoms were short-term reactions and disappeared on their own without the drug being withdrawn.

Discussion

We carried out the study of efficacy for PMNE treatment in two homogeneous groups of children using alarm intervention and desmopressin. Our results agree with data of other authors, and with our earlier observations on effectiveness of these treatment methods[17,18,21]. Group A: After the 16 month course of AI, symptoms of PMNE were absent in 82.7% of children and after another 2 months of observation in 74.7%. Group B: After the 16 month course of desmopressin, symptoms of PMNE were absent in 72.9% of children and after another 2 months of observation in 67.2%. Reduction in the percentage of patients with no symptoms of enuresis two months after the end of treatment is statistically not significant ($p>0.05$) and, in our opinion, may indicate good safety and stability of the therapeutic effect when using both AI and desmopressin.

Group A comprised 162 children treated with AI. At the end of the 4-month course, absence of PMNE was noted in 82.7% patients and after 6 months in 74.7% children. Group B comprised 177 children treated with desmopressin 0.4 mg/day 0.4 mg/day. In group B the absence of PMNE was noted 4 months after start of experiment in 72.9% of children and after six months in 67.2% of children.

However, the main purpose of this study was to determine possible predictors for treatment effectiveness among various anthropological, demographic, socio-economic and clinical factors. As a result of multivariate regression analysis, we found that the effectiveness of both methods of treatment depends on age. Among younger patients, the treatment was more effective, and the frequency of enuresis after treatment was significantly less than in 9-11 year children and 12-14 year old children ($p<0.05$). This result contradicts the data obtained by Van Herzeele et al. in 2015 in children receiving desmopressin[21]. The authors found better results among adolescents. However, the authors note that the selection was characterized by a low maximum volume of the urination, and an increased frequency of the urination, which probably indicates the presence of signs in children of overactive bladder (OAB). In our study, all children with signs of OAB were excluded from selection at the preliminary stage. At the same time, it is known that features of growth and development of the central nervous system provide a more effective consolidation of conditioned reflex connections at an early age. Perhaps this explains the best therapeutic effect in 6-8-year-olds in this study and in another study[23].

Many authors also pointed to severity of symptoms as a possible predictor of effective treatment[13,23]. In the presence of severe symptoms, both methods are equally effective, and even their combination[19]. However, treatment using AI was somewhat delayed, in comparison with the use of desmopressin[19]. This can be explained by the fact that desmopressin has a direct effect on the water balance within 30 minutes after administration. Action of AI is associated with the development of neural-reflex connections in response to an external stimulus and this requires, as a rule, several weeks.

A new and significant result of our study is the evidence that a high incidence of independent awakenings is associated with the significant decrease in the number of EE when applying AI, but does not affect the result of treatment among children taking desmopressin. In databases such as Scopus, WoS and PubMed, we were not able to locate studies on frequency of awakenings as an independent predictor for the effectiveness of PMNE. However, we can assume that children, who often awaken when urinating in a dream, already have a specific reflex arc, and parameters of sleep do not impede the realization of a conditioned reflex to awakening at full bladder. In this situation, only a small additional external stimulus is required to fix the existing conditioned reflex. At the same time, use of desmopressin increases the adaptive capacity, but does not affect the fixation of the conditioned reflex. In addition, we understand that this is only one possible explanation of the mechanisms for realizing the therapeutic effect and they certainly need further studies.

This study is not free of limitations. We did not investigate predictors of PMNE treatment effectiveness in individuals treated with the combination of AI and desmopressin, who received imipramine and some other alternative therapies. The range of investigated markers of the socio-economic and clinical status of patients was also incomplete. These issues require further study and interpretation.

Conclusions

Predictors of the successful treatment of PMNE with AI are high frequency of independent awakenings from urge to urinate, early age (6-8 years) and severity of symptoms. These predictors, with the exception of the high incidence of independent awakenings are favourable prognostic factors in making effective use of desmopressin. At the same time, the sex, presence of siblings, completeness of the family, level of family income, formation of parents, place of residence, clinical characteristics of urination have no significant influence on treatment outcomes of PMNE.

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